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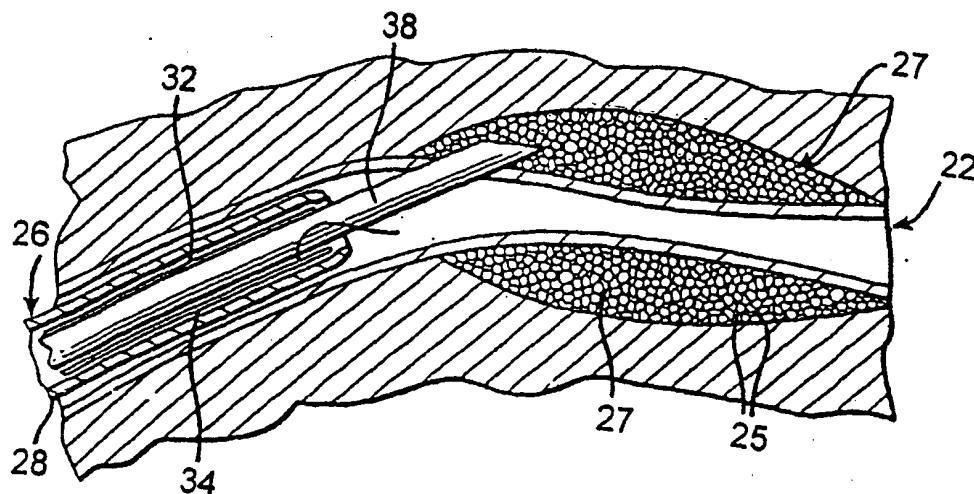
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(54) Title: TISSUE TREATMENT

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(57) Abstract: A method of treating tissue includes placing substantially spherical polymer particles in the tissue. The particles include an interior region having relatively large pores and a first region substantially surrounding the interior having fewer relatively large pores than the interior region.



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TISSUE TREATMENT

TECHNICAL FIELD

[0001] This invention relates to the treatment of tissue, such as the introduction of particles into body tissue for repair and/or augmentation.

BACKGROUND

[0002] The body includes various passageways through which bodily matter or fluids, such as urine, can flow. The flow of material through the passageways is in part affected by tissue surrounding the passageways. For example, the tissue can constrict and cause a passageway to narrow or to close, thereby restricting flow of material through the passageway.

[0003] In some disorders, the tissue can no longer affect a passageway. For example, while urine normally flows down in one direction from the kidneys, through tubes called ureters, and to the bladder, in vesicoureteral reflux (VUR), urine can flow abnormally from the bladder back into the ureters. In gastroesophageal reflux disease (GERD), sometimes called "reflux", acid from the stomach can flow back into the swallowing tube, or esophagus. Other disorders include, for example, urinary incontinence, i.e., loss of urinary control, and fecal incontinence.

[0004] One method of treating such disorders includes placing, e.g., injecting, a bulking material in the tissue adjacent to the passageway. The bulking material can narrow the passageway and, by providing bulk, allows the tissue to constrict the passageway more easily.

SUMMARY

[0005] This invention relates to the treatment of tissue.

[0006] In one aspect, the invention features a method of treating tissue including placing substantially spherical polymer particles in the tissue. The particles have an interior region having relatively large pores and a first region substantially surrounding the interior region having fewer relatively large pores than the interior region.

[0007] Embodiments may include one or more of the following features. The particles are injected into the tissue. The particles are injected percutaneously. The particles are delivered

through a catheter. The method includes forming a cavity in the tissue, and placing the particles in the cavity. The tissue is adjacent to a body passageway. The passageway is defined by a ureter. The tissue is adjacent to a body passageway, and the particles are placed in an amount effective to narrow the passageway.

[0008] The particles can be polyvinyl alcohol. The polyvinyl alcohol can be 1,3 diol acetalized. The particles can include a polysaccharide. The polysaccharide can include alginate.

[0010] The particles can include a therapeutic agent.

[0011] In another aspect, the invention features a method of treating an individual. The method includes placing a therapeutically effective amount of substantially spherical particles including polyvinyl alcohol in a tissue of the individual. The particles have an interior region having relatively large pores and a first region substantially surrounding the interior region having fewer relatively large pores than the interior region.

[0012] Embodiments can include one or more of the following features.

[0013] The method further includes selecting the individual diagnosed with gastroesophageal reflux disease. The tissue is adjacent to a gastrointestinal tract. The method further includes selecting the individual diagnosed with vesicoureteral reflux. The tissue is adjacent to a ureter.

[0014] The method can further include selecting an individual diagnosed with urinary incontinence, fecal incontinence, intrinsic sphincteric deficiency, and/or vocal cord paralysis. The method can further include selecting an individual in need of a reconstructive or cosmetic procedure.

[0015] The particles can be placed percutaneously and/or through a catheter.

[0016] In another aspect, the invention features a method of delivering a therapeutically effective amount of substantially spherical polymer particles. The particles include polyvinyl alcohol and include an interior region having relatively large pores and a surface region having fewer relatively large pores. The particles can have a diameter of about 1200 micron or less, a surface with a predominant pore size of about 2 micron or less and pores interior to the surface of about 10 micron or more, and/or a surface region from about 0.8r to r, the predominant pore size in the surface region being smaller than the predominant pore size in a region C to 0.3r.

[0017] Embodiments may also include one or more of the following. The relatively large pores are about 20 or 30 micron or more. The surface region is about r to $0.8r$. The surface region is about r to $2/3r$. The particles include a body region from about $2/3r$ to $r/3$ including intermediate size pores and the body region has more intermediate size pores than the surface region. The center region is from about $r/3$ to C , the outer region including large size pores and the body region has fewer large size pores than the center region. The intermediate size pores are about 2 to 18 microns. The surface region is substantially free of pores greater than about 5 micron.

[0018] Embodiments may also include one of the following. The predominant pore size progressively increases from surface to the center of the particle. The predominant pore size on the particle surface is about 1 micron or less. The particles have a surface region from about $(2r)/3$ to the surface wherein the predominant pore size is in the range of about 1 micron or less. The predominant pore size is about 0.1 micron or less. Interior of said surface region, the particles have a predominant pore size in the range of about 2 to 35 microns. The particles include a center region from about r to $r/3$ in which the predominant pore size is about 20 to 35 micron. The particles have a body region from $r/3$ to $(2r)/3$ in which the predominant pore size is about 2 to 18 micron. The particles have a surface region from about $(2r)/3$ to the periphery and the predominant pore size in the surface region is about 10% or less than the predominant pore size in the interior to the surface region. The particles include a surface region from about $0.8r$ to r wherein the predominant pore size is about 1 micron or less. The particles include a region from about C to $0.8r$ includes pores having a diameter of 10 microns or more. The region C to $0.8r$ has a predominant pore size of about 3.5 to 2 micron. The particles have a density of about 1.1 to about 1.4 g/cm³. The particles have a density of about 1.2 to 1.3 g/cm³. The particles have a sphericity of about 90% or more. The particles have an initial sphericity of about 97% or more. The particles have a sphericity of about 0.90 after compression to about 50%. The particles have a size uniformity of about + 15% or more.

[0019] Embodiments may also include one or more of the following. The particles include about 1% or less polysaccharide. The polysaccharide is alginate. The alginate has a guluronic acid content of about 60% or greater. The particles are substantially insoluble in DMSO. The particles are substantially free of animal-derived compounds. The polyvinyl

alcohol is composed of substantially unmodified polyvinyl alcohol prepolymer. The polyvinyl alcohol is predominantly intrachain 1, 3-diols acetalized. The composition includes saline and/or contrast agent. The particles and/or composition are sterilized.

[0020] Embodiments may also include one or more of the following. The gelling compound is a polysaccharide. The gelling compound is alginate. The alginate has a guluronic acid content of about 60% or more. The drops are contacted with a gelling agent. The gelling agent is a divalent cation. The cation is Ca⁺². The base polymer is PVA. The PVA is reacted by acetalization. The PVA has a molecular weight of about 75,000 g/mole or greater. The viscosity of the base polymer and gelling compound is modified prior to forming said drops. The viscosity is modified by heating. The drops are formed by vibratory nebulization.

[0021] Embodiments may also include one or more of the following. Administration is by percutaneous injection. Administration is by a catheter. The particles are introduced to the body through a lumen, and the lumen has a smaller diameter than the particles.

[0022] The particles can be tailored to a particular application by varying particle size, porosity gradient, compressibility, sphericity and density of the particles. The uniform size of the spherical particles can, for example, fit through the aperture of a needle or a catheter for administration by injection to a target site without partially or completely plugging the lumen of the needle or the catheter. Size uniformity of + 15% of the spherical particles allows the particles to stack evenly.

[0023] Embodiments may have one or more of the following advantages. The particles are relatively inert and biocompatible (e.g., they do not trigger an allergic or cytotoxic response). The particles do not substantially migrate, which can cause adverse effects. The particles are relatively non-bioresorbable. As a result, the particles retain their efficacy, and the need for repeated procedures is reduced, which can lower cost, trauma, and/or complications. The particles can be used in a variety of applications.

[0024] Other aspects, features, and advantages of the invention will be apparent from the description of the preferred embodiments thereof and from the claims.

DESCRIPTION OF DRAWINGS

[0025] Figs. 1A and 1B illustrate a method of treating tissue.

[0026] Fig. 2 illustrates a method of treating tissue.

[0027] Fig. 3A is a light micrograph of a collection of hydrated particles; Fig. 3B is a scanning electron microscope (SEM) photograph of the particle surface; and Figs. 3C-3E are cross-sections of the particles.

[0028] Fig. 4A is a schematic of the manufacture of a composition; and Fig. 4B is an enlarged schematic of region A in Fig. 4A.

[0029] Fig. 5 is a photograph of gel-stabilized drops.

[0030] Fig. 6 is a graph of particle size uniformity.

[0031] Figs. 7A-7F illustrate a method of treating tissue.

DETAILED DESCRIPTION

[0032] Referring to Figs. 1A and 1B, a method of treating tissue 20, here, located adjacent to a passageway 22, is shown. Passageway 22 is defined by a wall 24, e.g., of a urethra or a ureter. The method generally includes placing a composition 27 including highly water insoluble, high molecular weight polymer particles 25 into tissue 20. Particles 25, e.g., acetalized polyvinyl alcohol, have a substantially uniform shape and a symmetric compressibility. Particles 25 can increase bulk and localize compression, thereby reducing the size of passageway 22 and assisting tissue 20 in closing to reduce (e.g., minimize or eliminate) flow of matter, such as urine, through the passageway. As described below, composition 27 can include other materials, such as a carrier, a contrasting agent, and/or a therapeutic agent.

[0033] As shown, the method includes injecting composition 27 into tissue 20. Before composition 27 is injected, a cytoscope 26 is introduced into passageway 22 by conventional cytosopic techniques. Cytoscope 26 includes an elongated sheath 28 that defines a channel 30. In channel 30, cytoscope 26 includes a light emitting element 32 (such as an optic fiber) and a viewing element 34. Cytoscope 26 is positioned at a location selected to view a target area 36 to be treated.

[0034] Subsequently, a needle 38 is inserted into tissue 20 to target area 36, but without penetrating wall 24. Composition 27 including particles 25 is then injected from a syringe (not shown) to area 36. The progress of the injection can be monitored, for example, by viewing changes, e.g., narrowing, in passageway 22 through cytoscope 26 or by fluoroscopic or spectroscopic techniques, e.g., in embodiments in which composition 27 includes a contrasting agent (described below). In other embodiments, referring to Fig. 2, needle 38 is inserted through channel 30 of cytoscope 26 to deliver composition 27.

[0035] The methods described above can be used for a variety of medical applications, such as for the treatment of intrinsic sphincteric deficiency (ISD). For example, composition 27 can be used to treat urinary incontinence. Composition 27 can be injected into the tissue of the urinary tract, wherein the selected site can be, for example, the mucosal tissue of the bladder neck, the urethra or urethral sphincter. The resulting bulking or augmentation of the urethral tissue can reduce or restrict the size of the urethra or urinary passage and thus assist in overcoming incontinence. Methods and techniques of placing bulking materials for the treatment of urinary incontinence are described in Namiki, "Application of Teflon Paste for Urinary Incontinence – Report of Two Cases", *Urol. Int.*, Vol. 39, pp. 280-282 (1984); Politano et al., "Periurethral Teflon Injection for Urinary Incontinence", *The Journal of Urology*, Vol. 111, pp. 180-183 (1974); Winters, et al., "Periurethral Injection of Collagen in the Treatment of Intrinsic Sphincteric Deficiency in the Female Patient", *Urologic Clinics of North America*, 22(3):473-478 (1995); U.S. 5,007,940; U.S. 5,158,573; U.S. 5,116,387; and references cited therein.

[0036] Composition 27 can be injected into the tissue of the anal canal, wherein the selected site can be, for example, the mucosal tissue of the anal canal, such as near the internal or external anal sphincter muscle. The resulting bulking or augmentation of the tissue can restrict the size of the sphincter or anal passage and thus assist in reducing fecal or anal incontinence. Composition 27 can also be used to treat, e.g., repair, structurally defective and/or inadequately functioning muscles of the anal sphincter. For example, a physician can perianally inject composition 27 into a deformity, e.g., a keyhole deformity resulting from trauma or surgery, using one or more injections, until the deformity is repaired or the treated area is restored to its proper form. Methods of placing biocompatible materials to treat the sphincter muscles are described in Freed, U.S. 5,490,984.

[0037] Composition 27 can be used to treat vesicoureteral reflux. For example, composition 27 can be placed in the subureteral tissue to compress the ureter, thereby reducing the reflux of urine into the ureter. Methods for delivering a composition to treat vesicoureteral reflux are described in Capozza, et al., "Endoscopic Treatment of Vesico-Ureteric Reflux and Urinary Incontinence: Technical Problems in the Pediatric Patient," *Br. J. Urol.*, 75: 538-542 (1995); and Smith et al., "Evaluation of Polydimethylsiloxane as an Alternative in the Endoscopic Treatment of Vesicoureteral Reflux", *J. Urol.*, 152: 1221-1224, 1994.

[0038] Composition 27 can be applied to gastroesophageal reflux disease (GERD) applications. Composition 27 can be injected into the mucosal tissue of the upper gastrointestinal tract, wherein the selected site may be, for example, the mucosal tissue of the cardiac orifice of the stomach, which opens into the esophagus. The resulting bulking or augmentation of the tissue can restrict the size of the passage and thus assist in reducing gastric fluids refluxing into the esophagus. Methods and techniques are described, for example, in Shafik, "Intraesophageal Polytef Injection for the Treatment of Reflux Esophagitis", *Surg. Endoscopy*, 10:329-331 (1996), and references cited therein.

[0039] Composition 27 can also be used to treat other conditions, such as vocal cord paralysis, e.g., to restore glottic competence in cases of paralytic dysphonia. Such general treatment methods are described in Hirano et al., "Transcutaneous Intrafold Injection for Unilateral Vocal Cord Paralysis: Functional Results", *Ann. Otol. Rhinol. Laryngol.*, Vol. 99, pp. 598-604 (1990); Strasnick et al., "Transcutaneous Teflon® Injection for Unilateral Vocal Cord Paralysis: An Update", *Laryngoscope*, Vol. 101, pp. 785-787 (July 1991); and references cited therein.

[0040] In other embodiments, composition 27 is used to treat soft tissue. For example, composition 27 can be used for reconstructive or cosmetic applications, e.g., surgery. Examples of applications include reconstruction of cleft lips; scars, e.g., depressed scars from chicken pox or acne scars; indentations resulting from liposuction; wrinkles, e.g., glabella frown wrinkles; and soft tissue augmentation of thin lips. Composition 27 can be used as a graft material or a filler to fill and/or to smooth out soft tissue defects. For example, composition 27 can be injected percutaneously under a defect until the appearance of the defect, e.g., a wrinkle, is reduced. Procedures and techniques are describe, for example, in Ersek et al., "Bioplastique: A New Textured Copolymer Microparticles Promises

Permanence in Soft-Tissue Augmentation", *Plastic and Reconstructive Surgery*, Vol. 87, No. 4, pp 693-702 (April 1991); Lemperle et al., "PMMA Microspheres for Intradermal Implantation: Part I. Animal Research", *Annals of Plastic Surgery*, Vol. 26, No. 1, pp. 57-63 (1991); and references cited therein.

[0041] For the applications described above, the amount of composition 27 delivered can vary based on the nature, location and severity of the condition to be treated and the route of administration, the size of particles 25, and factors relating to the patient. A physician treating the condition, disease or disorder can determine an effective amount of composition 27. An effective amount of composition 27 refers to the amount sufficient to result in amelioration of symptoms or a prolongation of survival of the patient.

[0042] In other embodiments, particles 25 can also be used for implantable prostheses, such as mammary or breast implants, penile implants, or testicular prostheses. For example, particles 25 can be encased in a shell made of compliant material, such as silicone elastomers, polyolefins, polyurethanes, ethylene-propylene diene monomers, or ethylene-propylene rubbers. In embodiments, particles 25 can be used without a shell because they can remain at the delivery site and do not migrate. Prostheses are described, for example, in U.S. 5,941,909; U.S. 6,060,639; U.S. 5,063,914; and references cited therein.

[0043]

The Composition

[0044]

As described above, composition 27 includes polymer particles 25. In embodiments, composition 27 also includes a carrier, a contrasting agent, and/or a therapeutic agent.

[0045]

The particles: Particles 25 are substantially formed of polymer such as a highly water insoluble, high molecular weight polymer. As will be discussed below, a preferred polymer is high molecular weight polyvinyl alcohol (PVA) that has been acetalized. Preferably, the particles are substantially pure intrachain 1,3 acetalized PVA and substantially free of animal derived residue such as collagen. In embodiments, the particles include a minor amount, e.g. less than about 0.2 weight %, of alginate or another polysaccharide or gelling material.

[0046]

Referring to Fig. 3A, particles 111 have a substantially uniform spherical shape and size. Referring to Fig. 3B, each particle has a well-defined outer spherical surface including relatively small, randomly located pores. The surface appears substantially smooth, with some larger surface morphology such as crevice-like features. Referring to Figs. 3C-3E,

SEM images of cross-sections through particles, the body of the particle defines pores which provide compressibility and other properties. Pores near the center of the particle are relatively large and pores near the surface of the particle are relatively small.

[0047] The region of small pores near the periphery of the particle is relatively stiff and incompressible, which enhances resistance to shear forces and abrasion. In addition, the variable pore size profile produces a symmetric compressibility and, it is believed, a compressibility profile such that the particles are relatively easily compressed from a maximum, at rest diameter to a smaller, compressed first diameter but compression to even smaller diameter requires substantially greater force. A variable compressibility profile is believed to be due to the presence of a relative weak, collapsible inter-pore wall structure in the center region where the pores are large, and a stiffer inter-pore wall structure near the surface of the particle, where the pores are more numerous and relatively small. The variable pore size profile also is believed to enhance elastic recovery after compression. The pore structure also influences the density of the particles and the rate of carrier fluid or body fluid uptake.

[0048] The particles can be delivered through a needle having a lumen area that is smaller, e.g. 50% smaller or less, than the uncompressed cross-sectional area of the particles. As a result, the particles are compressed to pass through the needle for delivery into the body. The compression force is provided indirectly by increasing the pressure applied to the carrier fluid by depressing the syringe plunger. The particles are relatively easily compressed to diameters sufficient for delivery through the needle into the body. The robust, rigid surface region resists abrasion when the particles contact hard surfaces such as syringe surfaces, and the needle lumen wall (e.g. stainless steel) during delivery. Once in the body, the particles substantially recover to original diameter and shape, and form a dense mass. The compression can be limited by the compression profile of the particles, and the number of particles needed at a particular target area can be reduced.

[0049] In embodiments, the particles have a diameter of about 1500 or 1200 microns or less, and about 10 microns or more, e.g. about 400 microns or more and the pores are about 50 or 35 to 0.01 micron. The particles can be classified in size ranges of about 500-700 microns, about 700-900 microns, or about 900-1200 microns. The particles typically have a mean

diameter in approximately the middle of the range and variance of about 20% or less, e.g. 15% or 10% or less.

[0050] The particular size of the particles used can also be a function of their application. For example, for cosmetic applications, relatively small particles can be used to provide a more natural feel and to reduce a granular texture. Small particles can also be delivered through small needles, which can reduce psychological trauma and discomfort to the patient.

[0051] Referring particularly to Fig. 3C, the particles can be considered to include a center region, C, from the center of the particle to a radius of about $r/3$, a body region, B, from about $r/3$ to about $2r/3$ and a surface region, S, from $2r/3$ to r . The regions can be characterized by the relative size of the pores and the number of pores of given sizes. In embodiments, the center region has a greater number of relatively large pores than the body region and the surface region. The large pores are in the range of about 20 micron or more, e.g. 30 micron or more, or in the range of about 20 to 35 micron. The body region has a greater number of intermediate size pores than the surface region. The intermediate size pores are in the range of about 5 to 18 micron. In embodiments, the regions may also have different densities, with the density of the surface region being greater than the density of the body region, and the density of the body region being greater than the density of the center region.

[0052] The size of the pores in each of the regions can also be characterized by a distribution. In embodiments, the predominant pore size(s) in the center region being greater than the predominant pore size(s) in the body region and the predominant pore size(s) in the body region is greater than the predominant pore size(s) in the surface region. In embodiments, in the predominant pore size in the center region is 20 micron or more, e.g. 30 microns or more, or in the range of about 20 to 35 microns. The predominant pore size in the body region is about 18 micron or less, e.g. about 15 micron or less, or in the range of about 18 to 2 micron. The pores in the surface region are preferably predominantly less than about 1 micron, e.g. about 0.1 to 0.01 micron.

[0053] In embodiments, the predominant pore size in the body region is about 50 to 70% of the pore size in the center region and the pore size in the surface region is about 10% or less, e.g. about 2% of the pore size in the body region. The size of the pores on the outer surface of the particle is predominantly in the range of about 1 micron or less, e.g. about 0.1 or 0.01

micron. In embodiments, the surface and/or surface region is substantially free of pores having a diameter larger than about 10 micron or larger than about 1 micron. In embodiments, the predominant pore size is in the region 0.8 or 0.9r to r is about 1 micron or less, e.g. 0.5 to 0.1 micron or less. The region from the center of the particle to 0.8 or 0.9r has pores of about 10 micron or greater and/or has a predominant pore size of about 2 to 35 micron. In embodiments, the predominant pore size in the region 0.8 or 0.9r to r is about 5% or less, e.g. 1% or 0.3% or less than the predominant pore size in the region from the center to 0.9r. the largest pores in the particles can have a size in the range of 1% or 5% or 10% or more of the particle diameter.

[0054] The size of the pores can be measured by viewing a cross-section as in Fig. 3C. For irregularly shaped pores, the maximum visible cross-section is used. The predominant pore size(s) can be found by measuring the size of the visible pores and plotting the number of pores as a function of size. The predominant pore size(s) are the sizes that are about the maximum in the distribution. In Fig. 3C, the SEM was taken on wet particles including absorbed saline, which were frozen in liquid nitrogen and sectioned. (Fig. 3B was taken prior to sectioning.) In Figs. 3D and 3E, the particle was freeze-dried prior to sectioning and SEM analysis.

[0055] Referring to Fig. 4A, a system for manufacturing particles includes a flow controller 300, a drop generator 310, a gelling vessel 320, a reactor vessel 330, a gel dissolution chamber 340 and a filter 350. The flow controller 300 delivers polymer solutions to a viscosity controller 305, which heats the solution to reduce viscosity prior to delivery to the drop generator 310. The drop generator 310 forms and directs drops into a gelling vessel 320, where drops are stabilized by gel formation. The gel-stabilized drops are transferred from the gelling vessel 320 to reactor vessel 330 where the polymer in the gel-stabilized drops is reacted forming precursor particles. The precursor particles are transferred to a gel dissolution chamber 340, where the gel is dissolved. The particles are then filtered in a filter 350 to remove debris, sterilized, and packaged.

[0056] A base polymer and a gelling precursor are dissolved in water and mixed. The mixture is introduced to a high pressure pumping apparatus, such as a syringe pump (e.g., model PHD4400, Harvard Apparatus, Holliston, MA). Examples of base polymers include polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, poly vinyl sulfonate,

carboxymethyl cellulose, hydroxyethyl cellulose, substituted cellulose, polyacrylamide, polyethylene glycol, polyamides, polyureas, polyurethanes, polyester, polyethers, polystyrene, polysaccharide, polylactic acid, polyethylene, polymethylmethacrylate and copolymers or mixtures thereof. A preferred polymer is polyvinyl alcohol. The polyvinyl alcohol, in particular, is hydrolyzed in the range of 80 to 99%. The weight average molecular weight of the base polymer can be in the range of 9000 to 186,000, 85,000 to 146,000 or 89,000 to 98,000. Gelling precursors include, for example, alginates, alginate salts, xanthan gums, natural gum, agar, agarose, chitosan, carrageenan, fucoidan, furcellaran, laminaran, hypnea, eucheuma, gum arabic, gum ghatti, gum karaya, gum tragacanth, hyaluronic acid, locust beam gum, arabinogalactan, pectin, amylopectin, other water soluble polysaccharides and other ionically crosslinkable polymers. A particular gelling precursor is sodium alginate. A preferred sodium alginate is high guluronic acid, stem-derived alginate (e.g. about 50 or 60% or more guluronic acid with a low viscosity e.g. about 20 to 80 cps at 20°C) which produces a high tensile, robust gel. High molecular weight PVA is dissolved in water by heating, typically above about 70°C, while alginates can be dissolved at room temperature. The PVA can be dissolved by mixing PVA and alginate together in a vessel which is heated to autoclave temperature (about 121°C). Alternatively, the PVA can be disposed in water and heated and the alginate subsequently added at room temperature to avoid exposing the alginate to high temperature. Heat can also be applied by microwave application. In embodiments, for PVA/alginate, the mixture is typically about 7.5 to 8.5%, e.g. about 8% by weight PVA and about 1.5 to 2.5%, e.g. about 2%, by weight alginate.

[0057] Referring to Fig. 4B, the viscosity controller 305 is a heat exchanger circulating water at a predetermined temperature about the flow tubing between the pump and drop generator. The mixture of base polymer and gelling precursor flows into the viscosity controller 305, where the mixture is heated so that its viscosity is lowered to a level for efficient formation of very small drops. For a high molecular weight PVA/alginate solution, the temperature of the circulating water is less than about 75°C and more than about 60°C, for example, 65°C which maintains the mixture at a viscosity of 90-200 centipoise. For spherical particles, the viscosity of the drops is maintained so they are captured in the gelling vessel without splintering or cojoining which can create irregular, fibrous particles. In other embodiments,

the flow controller and/or the drop generator can be placed in a temperature-controlled chamber, e.g. an oven, or a heat tape wrap, to maintain a desired viscosity.

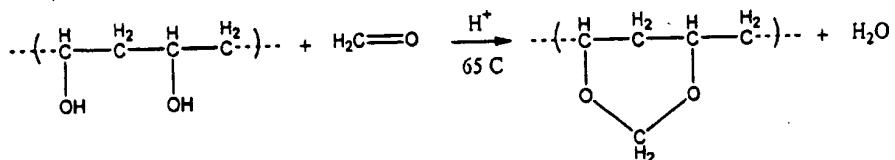
[0058] The drop generator 310 generates substantially spherical drops of predetermined diameter by forcing a stream of the mixture of base polymer and gelling precursor through a nozzle which is subject to a periodic disturbance to break up the jet stream into drops. The jet stream can be broken into drops by vibratory action generated for example, by an electrostatic or piezoelectric element. The drop size is controlled by controlling the flow rate, viscosity, amplitude, and frequency at which the element is driven. Lower flow rates and higher frequencies produce smaller drops. A suitable electrostatic drop generator is available from NISCO Engineering, model NISCO Encapsulation unit VAR D, Zurich, Switzerland. In embodiments, the frequency is in the range of about 0.1 to 0.8 kHz. The flow rate through the droplet generator is in the range of about 1 to 12 mL per minute. The drop generator can include charging the drops after formation such that mutual repulsion between drops prevents drop aggregation as drops travel from the generator to the gelling vessels. Charging may be achieved by, e.g. an electrostatic charging device such as a charged ring positioned downstream of the nozzle.

[0059] Drops of the base polymer and gelling precursor mixture are captured in the gelling vessel 320. The gelling vessel 320 contains a gelling agent which interacts with the gelling precursor to stabilize drops by forming a stable gel. Suitable gelling agents include, for example, a divalent cation such as alkali metal salt, alkaline earth metal salt or a transition metal salt that can ionically crosslink with the gelling agent. An inorganic salt, for example, a calcium, barium, zinc or magnesium salt can be used as a gelling agent. In embodiments, particularly those using an alginate gelling precursor, a suitable gelling agent is calcium chloride. The calcium cations have an affinity for carboxylic groups in the gelling precursor. The cations complex with carboxylic groups in the gelling precursor resulting in encapsulation of the base polymer in a matrix of gelling precursor.

[0060] Referring to Fig. 5, a photo-image of the gelled particles, the gelling agent is in an amount selected in accordance with the desired properties of the particles. As evident, a pore structure in the particle forms in the gelling stage. The concentration of the gelling agent can control pore formation in the particle, thereby controlling the porosity gradient in the particle. Adding non-gelling ions, for example, sodium ions, to the gelling solution can reduce the

porosity gradient, resulting in a more uniform intermediate porosity throughout the particle. In embodiments, the gelling agent is, for example, 0.01-10 weight percent, 1-5 weight percent or 2 weight percent in deionized water. In embodiments, particles, including gelling agent and a pore structure can be used in composition 27.

[0061] Following drop stabilization, the gelling solution is decanted from the solid drops and the stabilized drops are transferred to the reactor vessel 330. In the reactor vessel 330, the stabilized drops are reacted to produce precursor particles. The reactor vessel includes an agent that chemically reacts with the base polymer, e.g. to cause crosslinking between polymer chains and/or within a polymer chain. The agent diffuses into the stabilized drops from the surface of the particle in a gradient which, it is believed, provides more crosslinking near the surface of the stabilized drop compared to the body and center of the drop. Reaction is greatest at the surface of the drop, providing a stiff, abrasion resistant exterior. For polyvinyl alcohol, for example, the vessel 330 includes aldehydes, such as formaldehyde, glyoxal, benzaldehyde, aterephthalaldehyde, succinaldehyde and glutaraldehyde for the acetalization of polyvinyl alcohol. The vessel 330 also includes an acid, for example, strong acids such as sulfuric acid, hydrochloric acid, nitric acid and weak acids such as acetic acid, formic acid and phosphoric acid. In embodiments, the reaction is primarily a 1,3 acetalization:



[0062] This intra-chain acetalization reaction can be carried out with relatively low probability of inter-chain crosslinking as described in John G. Pritchard "Poly(Vinyl Alcohol) Basic Properties And Uses (Polymer Monograph, vol. 4) (see p. 93-97), Gordon and Breach, Science Publishers LTD., London, 1970, the entire contents of which is hereby incorporated by reference. Some OH groups along a polymer chain can remain unconverted since the reaction proceeds in a random fashion and there can be left over OH groups that do not react with adjacent groups.

[0063] Adjusting the amount of aldehyde and acid used, reaction time and reaction temperature can control the degree of acetalization. In embodiments, the reaction time is

e.g., 5 minutes to 1 hour, 10 to 40 minutes or 20 minutes. The reaction temperature can be 25 °C to 150 °C or 75 °C to 130 °C or 65 °C. The reactor vessel is placed in a water bath fitted with an orbital motion mixer. The crosslinked precursor particles are washed several times with deionized water to neutralize the particles and remove any residual acidic solution.

[0064] The precursor particles are transferred to the dissolution chamber 340 to remove the gelling precursor, e.g. by an ion exchange reaction. In embodiments, sodium alginate is removed by ion exchange with a solution of sodium hexa-metaphosphate (EM Science). The solution can include, for example, ethylenediaminetetraacetic acid (EDTA), citric acid, other acids and phosphates. The concentration of the sodium hexa-metaphosphate can be, for example, 1-20 weight %, 1-10 weight % or 5 weight % in deionized water. Residual gelling precursor, for example, sodium alginate, can be determined by assay for detection of uronic acids in, for example, alginates containing mannuronic and guluronic acid residues. Suitable assays include rinsing the particles with sodium tetraborate in sulfuric acid solution to extract alginate and combining the extract with metahydroxydiphenyl colormetric reagent and determining concentration by UV/VIS spectroscopy. Testing can be carried out by alginate suppliers such as FMC Biopolymer, Oslo, Norway. Residual alginate can be present in the range of about 20-35% by weight prior to rinsing and in the range of about 0.01-0.5% or 0.1-0.3% or 0.18% in the particles after rinsing for 30 minutes in water at about 23°C.

[0065] The particles are filtered through filter 350 to remove residual debris. Particles of 500 to 700 microns are filtered through a sieve of 710 microns and then a sieve of 300 microns. Particles of 700 to 900 microns are filtered through a sieve of 1000 microns and then a sieve of 500 microns. Particles of 900 to 1200 microns are filtered through a sieve of 1180 microns and then a sieve of 710 microns.

[0066] The filtered particles are sterilized by a low temperature technique such as e-beam irradiation, and packaged. In embodiments, electron beam irradiation can be used to pharmaceutically sterilize the particles to reduce bioburden. In e-beam sterilization, an electron beam is accelerated using magnetic and electric fields, and focused into a beam of energy. This resultant beam can be scanned by means of an electromagnet to produce a "curtain" of accelerated electrons. The accelerated electron beam penetrates the collection of particles to confer upon them electrons which destroy bacteria and mold to sterilize and

reduce the bioburden in the particles. Electron beam sterilization can be performed by sterilization vendors, such as Titan Scan, Lima, Ohio.

[0067] Additional information about the particles is described in commonly assigned U.S.S.N. [Attorney Docket No. 01194-442001], filed August 9, 2002, and entitled "Embolization", hereby incorporated by reference in its entirety.

[0068] The following example is illustrative and not intended to be limiting.

[0069]

Example

[0070] Particles are manufactured from an aqueous solution containing 8 weight % of polyvinyl alcohol, 99+% hydrolyzed, average M_w 89,000-120,000 (ALDRICH) and 2 weight% of gelling precursor, sodium alginate, PRONOVA UPLVG, (FMC BioPolymer, Princeton, NJ) in deionized water and the mixture is heated to about 121 °C. The solution has a viscosity of about 310 centipoise at room temperature and a viscosity of about 160 cps at 65°C. Using a syringe pump (Harvard Apparatus), the mixture is fed to drop generator (Nisco Engineering). Drops are directed into a gelling vessel containing 2 weight % of calcium chloride in deionized water and stirred with a stirring bar. The calcium chloride solution is decanted within about three minutes to avoid substantial leaching of the polyvinyl alcohol from the drops into the solution. The drops are added to the reaction vessel containing a solution of 4% by weight of formaldehyde (37 wt% in methanol) and 20% by weight sulfuric acid (95-98% concentrated). The reaction solution is stirred at 65°C for 20 minutes. Precursor particles are rinsed with deionized water (3 X 300 mL) to remove residual acidic solution. The sodium alginate is substantially removed by soaking the precursor particles in a solution of 5 weight % of sodium hexa-methaphosphate in deionized water for 0.5 hour. The solution is rinsed in deionized water to remove residual phosphate and alginate. The particles are filtered by sieving, as discussed above, placed in saline (USP 0.9% NaCl) and followed by irradiation sterilization.

[0071] Particles were produced at the nozzle diameters, nozzle frequencies and flow rates (amplitude about 80% of maximum) described in Table 1.

TABLE 1

| Bead Size (microns) | Nozzle Diameter (microns) | Frequency (kHz) | Flow Rate (mL/min) | Density (g/mL) | Sphericity | Suspendability (minutes) |
|------------------------|---------------------------------|--------------------|-----------------------|-------------------|------------|-----------------------------|
| 500-700 | 150 | 0.45 | 4 | - | 0.92 | 3 |
| 700-900 | 200 | 0.21 | 5 | 1.265 | 0.94 | 5 |
| 900-1200 | 300 | 0.22 | 10 | - | 0.95 | 6 |

[0072] Suspendability is measured at room temperature by mixing a solution of 2 ml of particles in 5 ml saline with contrast solution (Omnipaque 300, Nycomed, Buckinghamshire, UK) and observing the time for about 50% of the particles to enter suspension, i.e. have not sunk to the bottom or floated to the top of a container (about 10 ml, 25 mm diameter vial). Suspendability provides a practical measure of how long the particles will remain suspended. (Omnipaque is an aqueous solution of Iohexol, N.N.-Bis (2,3-dihydroxypropyl)-T-[N-(2,3-dihydroxypropyl)-acetamide]-2,4,6-trilodo-isophthalamide; Omnipaque 300 contains 647 mg of iohexol equivalent to 300 mg of organic iodine per ml. The specific gravity of 1.349 of 37 °C and an absolute viscosity 11.8 cp at 20 °C.) The particles remain in suspension for about 2 to 3 minutes.

[0073] Particle size uniformity and sphericity is measured using a Beckman Coulter RapidVUE Image Analyzer version 2.06 (Beckman Coulter, Miami, FL). Briefly, the RapidVUE takes an image of continuous-tone (gray-scale) form and converts it to a digital form through the process of sampling and quantization. The system software identifies and measures particles in an image in the form of a fiber, rod or sphere. Sphericity computation and other statistical definitions are in Appendix A, attached, which is a page from the RapidVUE operating manual.

[0074] Referring to Fig. 6, particle size uniformity is illustrated for particles 700 – 900 micron. The x-axis is the particle diameter. The y-axis is the volume normalized percentage of particles at each particle size. The total volume of particles detected is computed and the volume of the particles at each diameter is divided by the total volume. The particles have distribution of particle sizes with variance of less than about $\pm 15\%$.

[0075] While substantially spherical particles are preferred, non-spherical particles can be manufactured and formed by controlling, e.g., drop formation conditions or by post-processing the particles, e.g. by cutting or dicing into other shapes. Particles can also be

shaped by physical deformation followed by crosslinking. Particle shaping is described in U.S. Serial No. 10/116,330, filed April 4, 2002.

[0076] **Carrier:** Composition 27 can include one or more carrier materials that allow the composition to be delivered in a first state, e.g., a relatively fluid or low viscosity state, and change, e.g., by phase transition, to a second state, e.g., a relatively high viscosity or rigid state. In embodiments, particles 25 can be suspended in a biocompatible, resorbable lubricant, such as a cellulose polysaccharide gel having water, glycerin and sodium carboxymethylcellulose. The gel enables particles 25 to remain in suspension without settling. Other polysaccharides can also be included such as cellulose, agar methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, microcrystalline cellulose, oxidized cellulose, and other equivalent materials.

[0077] The polysaccharide gel is biocompatible, and the lubricious nature of the polysaccharide gel can reduce the frictional forces generated during the transferring of the particles from a syringe by injection into the tissue site. In addition, polysaccharides do not generate an antigenic response, and the polysaccharide gel is readily sterilizable and stable at ambient conditions and does not need refrigeration for storage and shipment.

[0078] After injection of composition 27 into the tissue, the polysaccharide gel can be resorbed by the tissue, leaving the non-resorbable matrix of particles 25 in place in the particular area or bolus, where it can remain without migrating to other areas of the body.

[0079] Other examples of carriers include undiluted agarose, methyl cellulose or other linear unbranched polysaccharide, dextran sulfate, succinylated non-crosslinked collagen, methylated non-crosslinked collagen, glycogen, dextrose, maltose, triglycerides of fatty acids, egg yolk phospholipids, heparin, DMSO, phosphate buffered saline, and the like. Examples of collagen are described in U.S. 5,490,984. More examples of appropriate carriers include hyaluronic acid, polyvinyl pyrrolidone or a hydrogel derived thereof, dextran or a hydrogel derivative thereof, glycerol, polyethylene glycol, succinylated collagen, liquid collagen, oil based emulsions such as corn oil or safflower, B-D glucose (or B-glucan, as described in U.S. 6,277,392) or other polysaccharides or biocompatible organic polymers either singly or in combination with one or more of the above materials.

[0080] Hydrogel compositions, such as those that swell upon injection into tissue due to hydration by physiologic fluid, are described, for example, in U.S. 6,423,332; U.S.

6,306,418; and 5,902,832. In embodiments, the composition can swell from an initial dehydrated volume to a final hydrated volume that is substantially the same as the initial total volume of composition injected into the tissue to be treated. Examples include poly(ethylene oxide), polyvinyl pyrrolidone, polyvinyl alcohol, poly(propylene oxide), poly(ethylene, glycol), poly(propylene glycol), polytetramethylene oxide, polyacrylamide, poly(hydroxy ethyl acrylate), poly(hydroxy ethyl methacrylate), hydroxy ethyl cellulose, hydroxy propyl cellulose, methoxylated pectin gels, agar, a starch such as cornstarch, a modified starch, an alginate, a hydroxy ethyl carbohydrate, or the like and should preferably be adjusted so as to allow swelling to a selected percent after hydration. The carrier can disperse over time.

[0081] In some embodiments, composition 27 includes between about 0.5 to about 50 weight percent of the carrier. For example, composition 27 can include greater than or equal to about 0.5, 5, 10, 15, 20, 25, 30, 35, 40, or 45 weight percent of the carrier; and/or less than or equal to about 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 weight percent of the carrier.

[0082] Contrasting agent: In embodiments, composition 27 includes a contrasting agent. The contrast agent can be a biocompatible material capable of being monitored during injection by, for example, radiography, fluoroscopy, ultrasound, or visually. The contrast agent can be water soluble or water insoluble. Examples of water soluble contrast agents include metrizamide, iopamidol, iothalamate sodium, iodomide sodium, and meglumine. Examples of water insoluble contrast agents include tantalum, tantalum oxide, and barium sulfate, each of which is available in a form for in vivo use including a particle size of about 10 microns or less. Other water insoluble contrast agents include gold, tungsten, and platinum powders.

[0083] Some examples of radiopaque materials include paramagnetic materials (e.g. persistent free radicals) and compounds, salts, and complexes of paramagnetic metal species (e.g., transition metal or lanthanide ions); heavy atom (e.g., atomic number of 37 or more) compounds, salts, or complexes (e.g., heavy metal compounds, iodinated compounds, etc.); radionuclide-containing compounds, salts, or complexes (e.g. salts, compounds or complexes of radioactive metal isotopes or radiiodinated organic compounds); and superparamagnetic materials (e.g., metal oxide or mixed oxide particles, particularly iron oxides). Paramagnetic metals include Gd (III), Dy (III), Fe (II), Fe (III), Mn (III) and Ho (III), and paramagnetic Ni, Co and Eu species. Heavy metals include Pb, Ba, Ag, Au, W, Cu, Bi and lanthanides such as

Gd. Metals, metal oxides, and alloys, including but not limited to medical grade stainless steel, silver, gold, titanium and titanium alloys, oxide derivatives of stainless steel or titanium or titanium alloys, aluminum oxide, and zirconium oxide can also be used. The amount of contrasting agent used can be any amount sufficient to be detected.

[0084] Therapeutic agent: In embodiments, particles 25 include one or more therapeutic agents. For example, an effective amount of wound healing agents can be added to composition 27. These agents include protein growth factors such as fibroblast growth factors (FGFs), platelet derived growth factors (PDGFs), epidermal growth factors (EGFs), connective tissue activated peptides (CTAPs), transforming growth factors (TGFs), and the like. The amount of wound healing agent(s) to be included with composition 27 can vary, depending, for example, on the patient (age, sex, medical history) and the site being treated. In embodiments, composition 27 includes antimicrobial additives and/or antibodies to reduce the potential for infection at the treatment site. Other agents are described in commonly assigned U.S.S.N. _____ [Attorney Docket No. 01194-438001], filed on August 30, 2002, and entitled "Drug Delivery Particles". The therapeutic agent can be added to composition 27 and/or be placed on particles 25.

[0085] Other additives: Composition 27 can include one or more materials that enhance the mechanical and/or physical properties of the composition. In some embodiments, particles 25 can be combined with one or more relatively hard materials. The relatively hard material can be, for example, biocompatible ceramics, biocompatible metals (e.g., stainless steel), glass, or other biocompatible materials such as calcium salts, e.g., hydroxyapatite. The combination of particles 25 and hard material(s) can be used, for example, to fill depressed scars, unsymmetrical orbital floors, or bone defects in reconstructive surgical procedures.

[0086] Other methods can be used to place particles 25 and/or composition 27 into tissue. For example, particles 25 and/or composition 27 can be placed laproscopically. Particles 25 and/or composition 27 can also be placed in a cavity or void created in tissue.

[0087] Referring to Figs. 7A-7F, a method of placing particles 25 and/or composition 27 is shown. The method includes using a catheter or a sheath 402, e.g., a blunt-ended hypotube, configured to proximally receive a penetration device 404, e.g., one having a trocar at its distal end. Penetration device 404 is inserted into sheath 402 to allow the sheath to penetrate into tissue 403 (Fig. 7A). In embodiments, the penetration depth can be determined by

striping 406 formed on sheath 402. For example, the tip of penetration device 404 can penetrate about 2-2.5 cm into tissue 403, while the tip of sheath 402 can penetrate about 0.5-1 cm into the tissue. After penetration of tissue 403, penetration device 404 is withdrawn from sheath 402, which is retained penetrated in the tissue (Fig. 7B).

[0088] A catheter 406 carrying an uninflated balloon 408 at the distal end is then inserted into sheath 402 (Fig. 7C) such that the balloon extends into tissue 403. Balloon 408 is then inflated using an inflation device, such as a syringe 410 containing saline (Fig. 7D). As balloon 408 inflates, it creates a cavity or a void 412 in tissue 403. In embodiments, balloon 408 is shaped to provide a cavity with a predetermined shape. Balloon 408 is then deflated, and catheter 406 is withdrawn from sheath 402 (Fig. 7E). An injection device 414, such as a syringe 416 containing particles 25 and/or composition 27, is then inserted into sheath 402, and the particles and/or composition can be delivered to cavity 412 (Fig. 7F).

[0089] In other embodiments, particles 25 and/or composition 27 can be used with a device, such as an indwelling sling, used to treat urinary incontinence. An example of a device is described in WO 00/74633. Particles 25 and/or composition 27 can be placed, e.g., injected, into the device as a bulking agent to provide lift, thereby providing another method of adjusting the degree of support provided by the device.

[0090] All publications, references, applications, and patents referred to herein are incorporated by reference in their entirety.

[0091] Other embodiments are within the claims.

WHAT IS CLAIMED IS:

1. A method of treating tissue, the method comprising:
placing substantially spherical polymer particles in the tissue, the particles having an interior region comprising relatively large pores and a first region substantially surrounding the interior region comprising fewer relatively large pores than the interior region.
2. The method of claim 1, wherein the particles are injected into the tissue.
3. The method of claim 2, wherein the particles are injected percutaneously.
4. The method of claim 1, wherein the particles are delivered through a catheter.
5. The method of claim 1, comprising forming a cavity in the tissue, and placing the particles in the cavity.

6. The method of claim 1, wherein the tissue is adjacent to a body passageway.
7. The method of claim 6, wherein the passageway is defined by a ureter.
8. The method of claim 1, wherein the tissue is adjacent to a body passageway, the particles being placed in an amount effective to narrow the passageway.
9. The method of claim 1, wherein the particles comprise polyvinyl alcohol.
10. The method of claim 9, wherein the polyvinyl alcohol is 1,3 diol acetalized.
11. The method of claim 9, wherein the particles comprise a polysaccharide.
12. The method of claim 9, wherein the polysaccharide comprises alginate.

13. The method of claim 1, wherein the particles comprise a therapeutic agent.
14. A method of treating an individual, the method comprising:
placing a therapeutically effective amount of substantially spherical particles comprising polyvinyl alcohol in a tissue of the individual, the particles having an interior region comprising relatively large pores and a first region substantially surrounding the interior region comprising fewer relatively large pores than the interior region.
15. The method of claim 14, further comprising selecting the individual diagnosed with gastroesophageal reflux disease.
16. The method of claim 15, wherein the tissue is adjacent to a gastrointestinal tract.
17. The method of claim 14, further comprising selecting the individual diagnosed with vesicoureteral reflux.
18. The method of claim 17, wherein the tissue is adjacent to a ureter.
19. The method of claim 14, further comprising selecting the individual diagnosed with urinary incontinence.
20. The method of claim 14, further comprising selecting the individual diagnosed with fecal incontinence.
21. The method of claim 14, wherein the particles are placed percutaneously.
22. The method of claim 14, wherein the particles are placed through a catheter.
23. The method of claim 14, further comprising selecting the individual diagnosed with intrinsic sphincteric deficiency.

24. The method of claim 14, further comprising selecting the individual diagnosed with vocal cord paralysis.

25. The method of claim 14, further comprising selecting the individual in need of a reconstructive or cosmetic procedure.

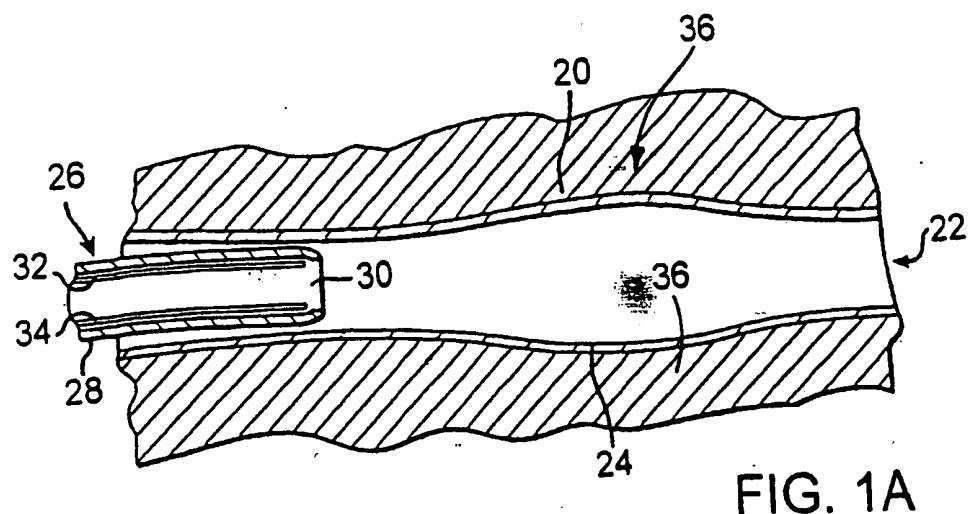


FIG. 1A

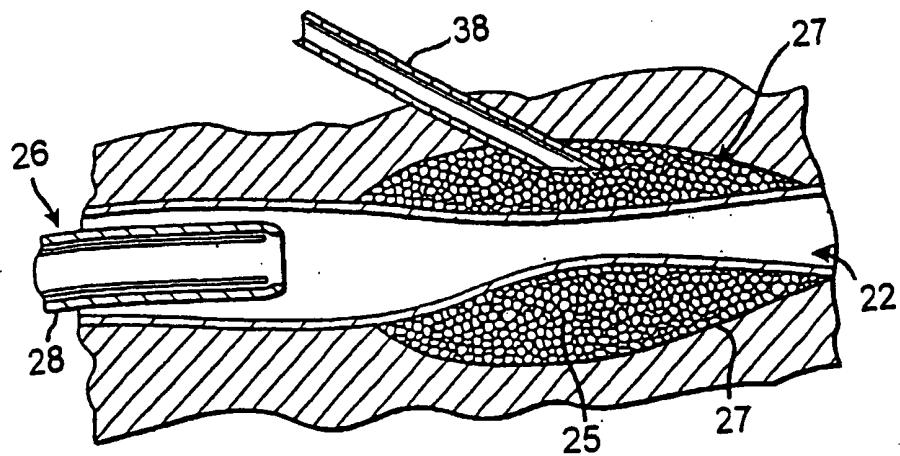


FIG. 1B

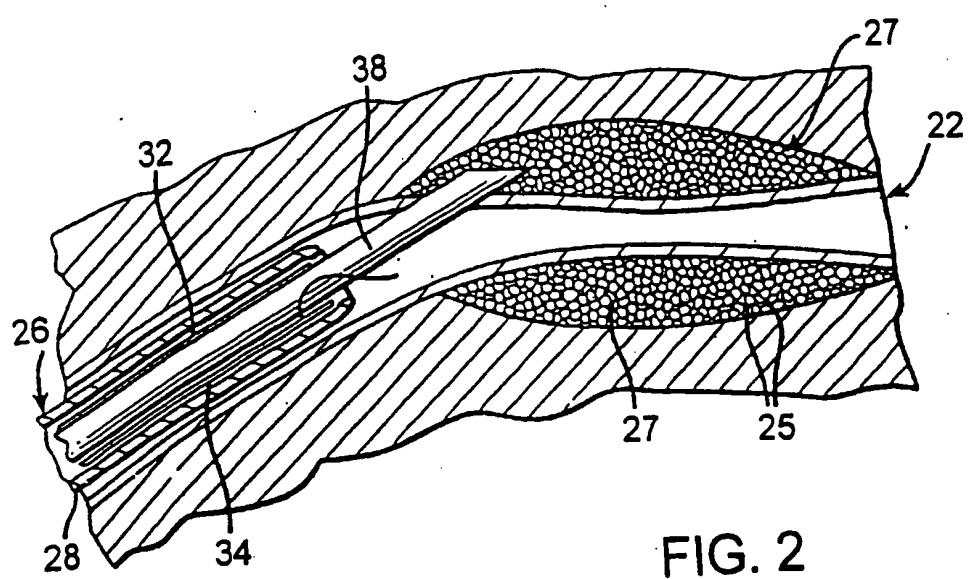


FIG. 2

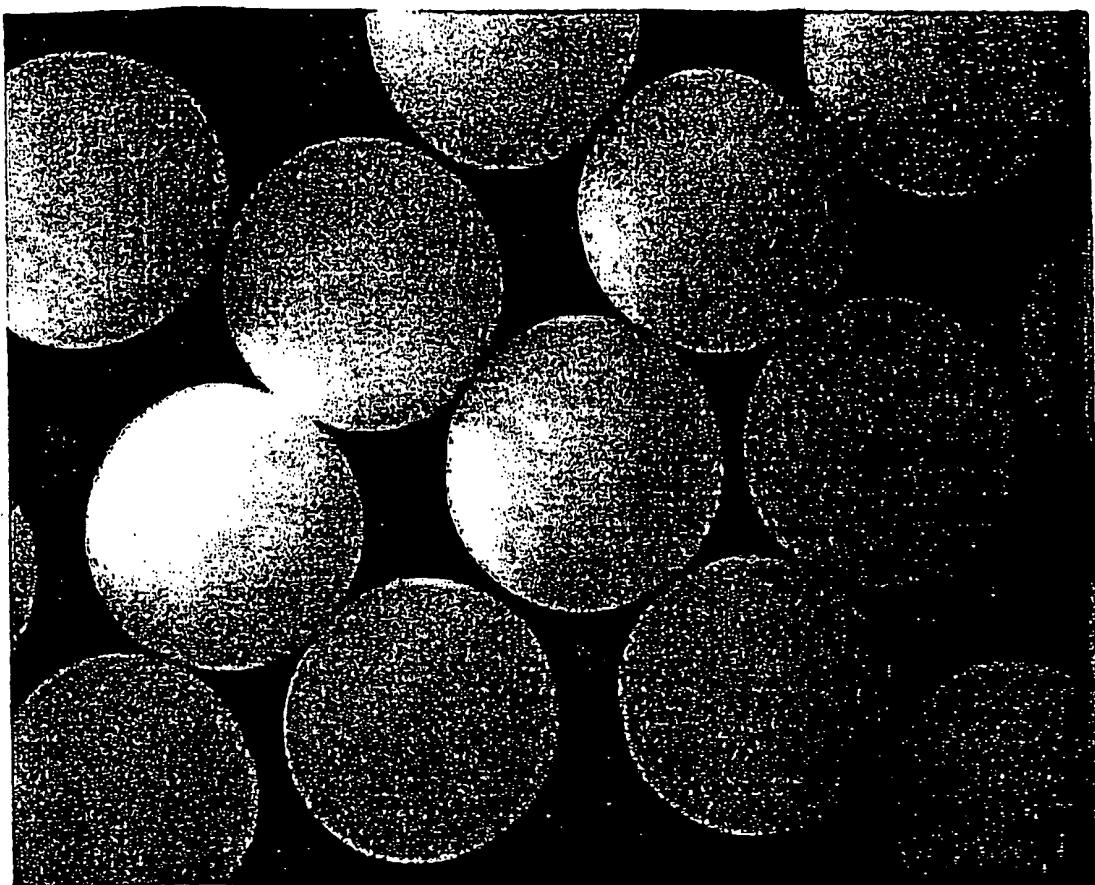


FIG. 3A

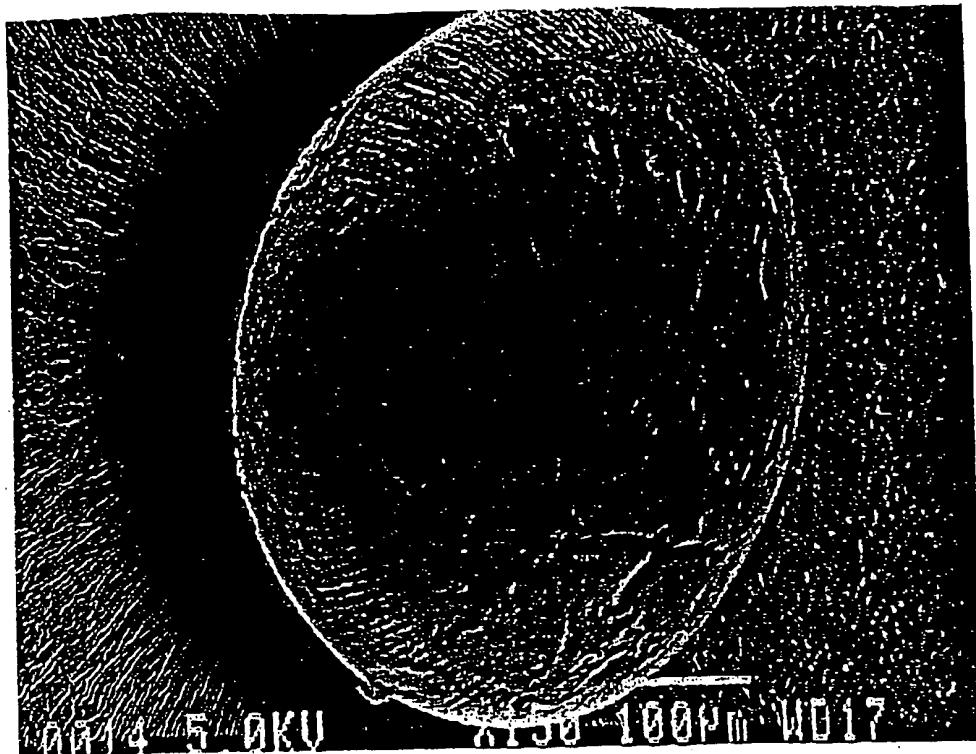


FIG. 3B

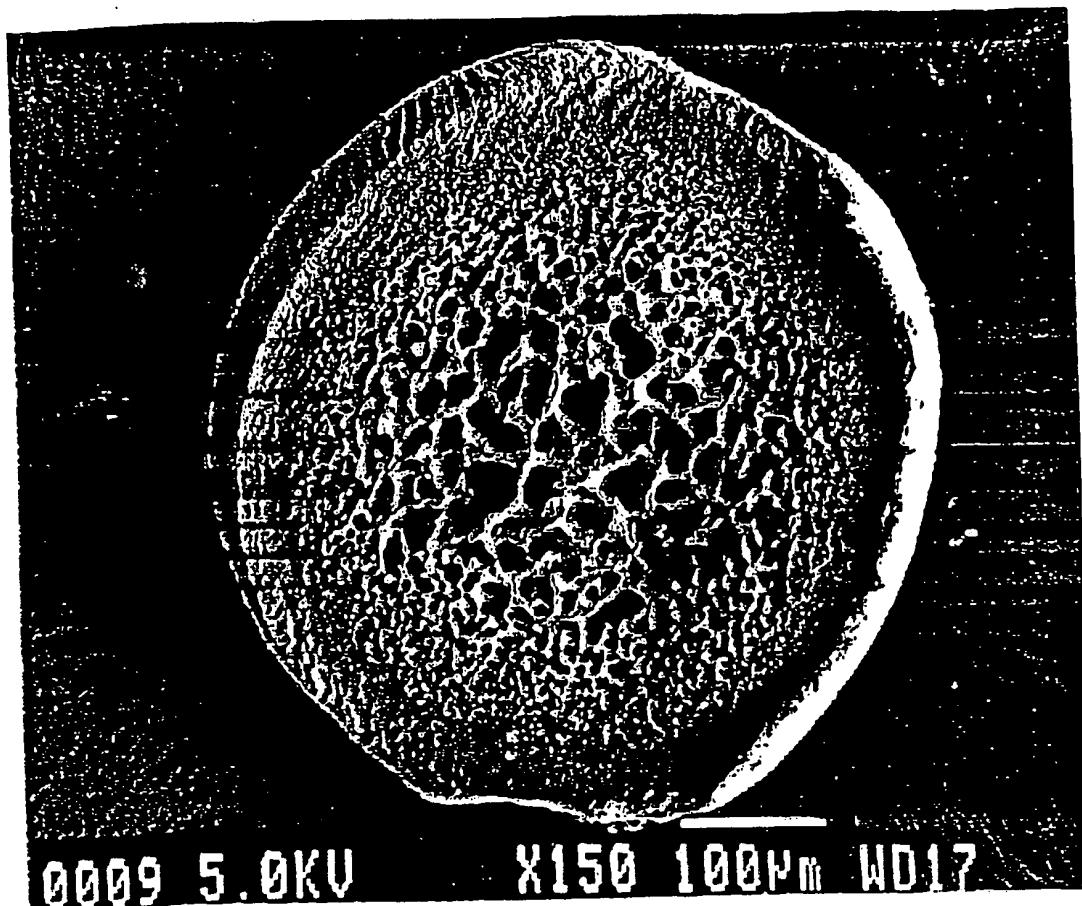


FIG. 3C

| | | |
r 2r/3 r/3 c

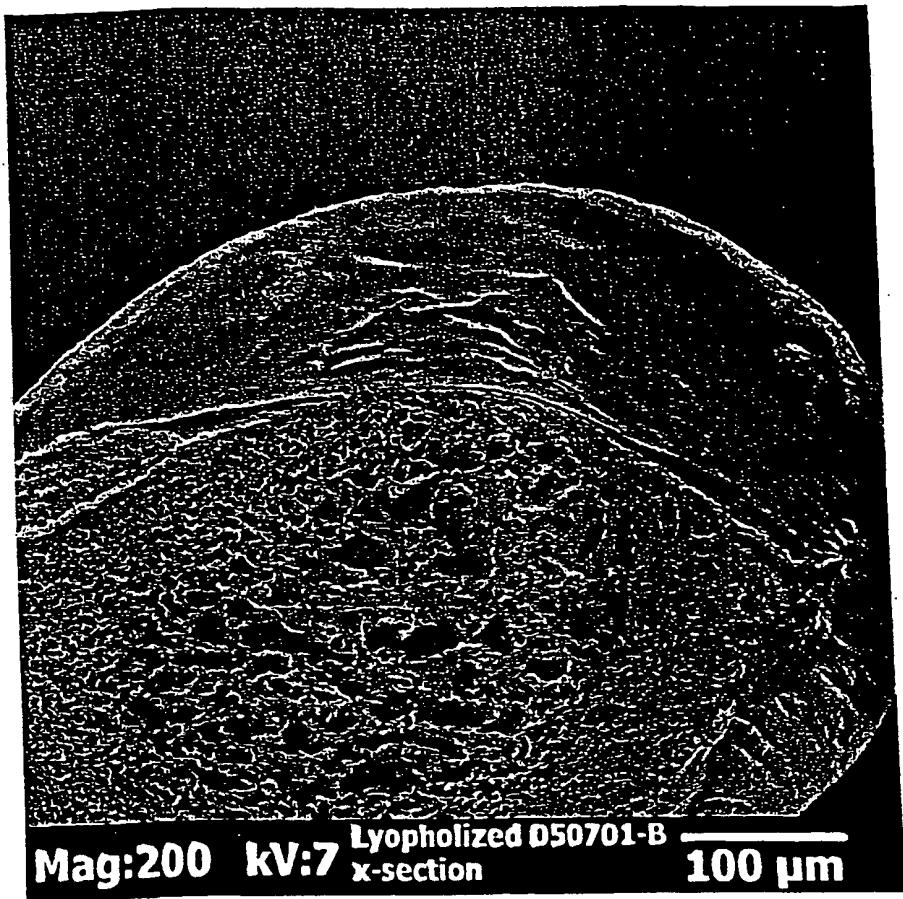


FIG. 3D

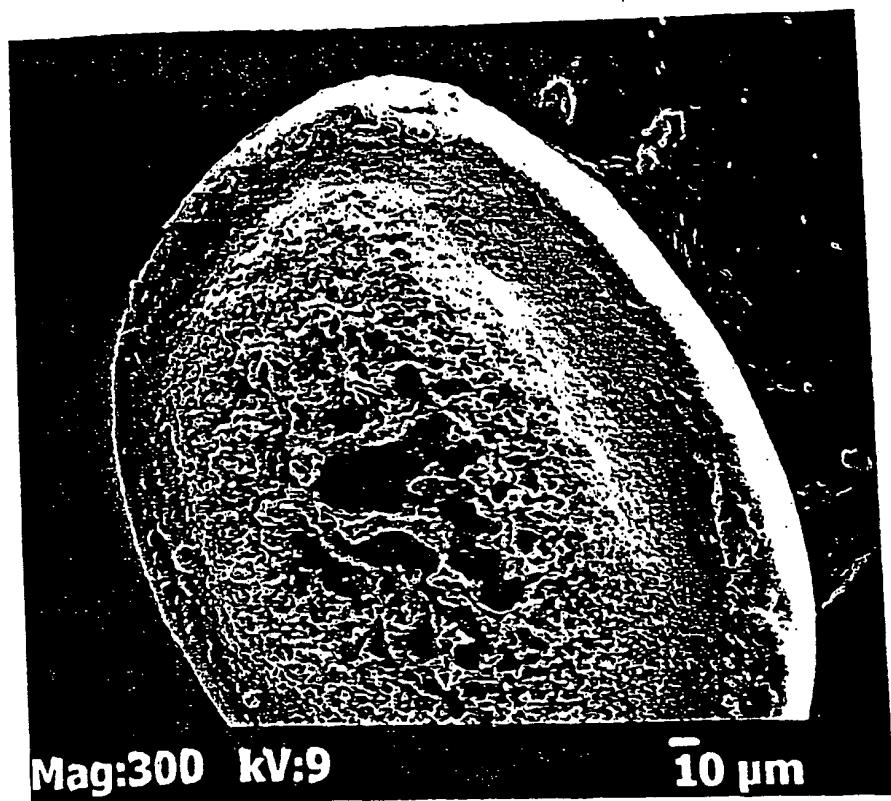


FIG. 3E

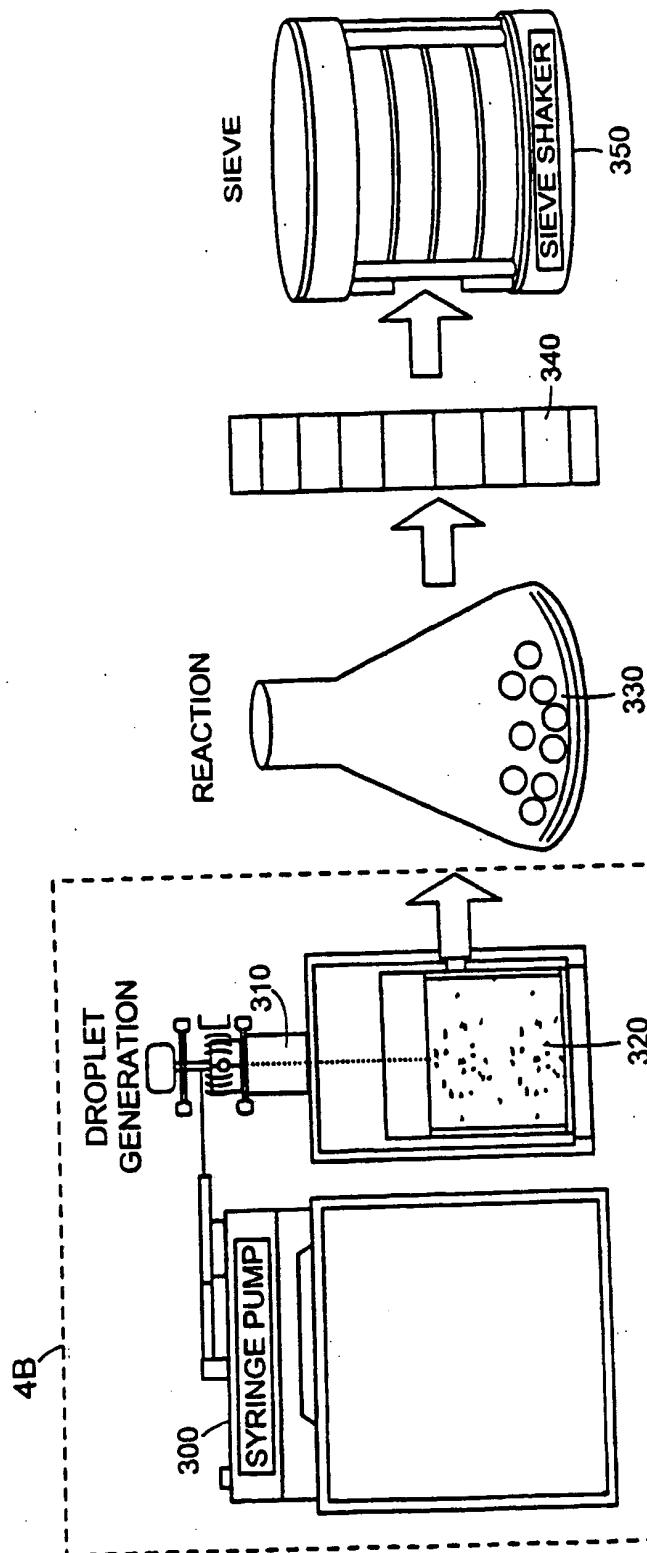


FIG. 4A

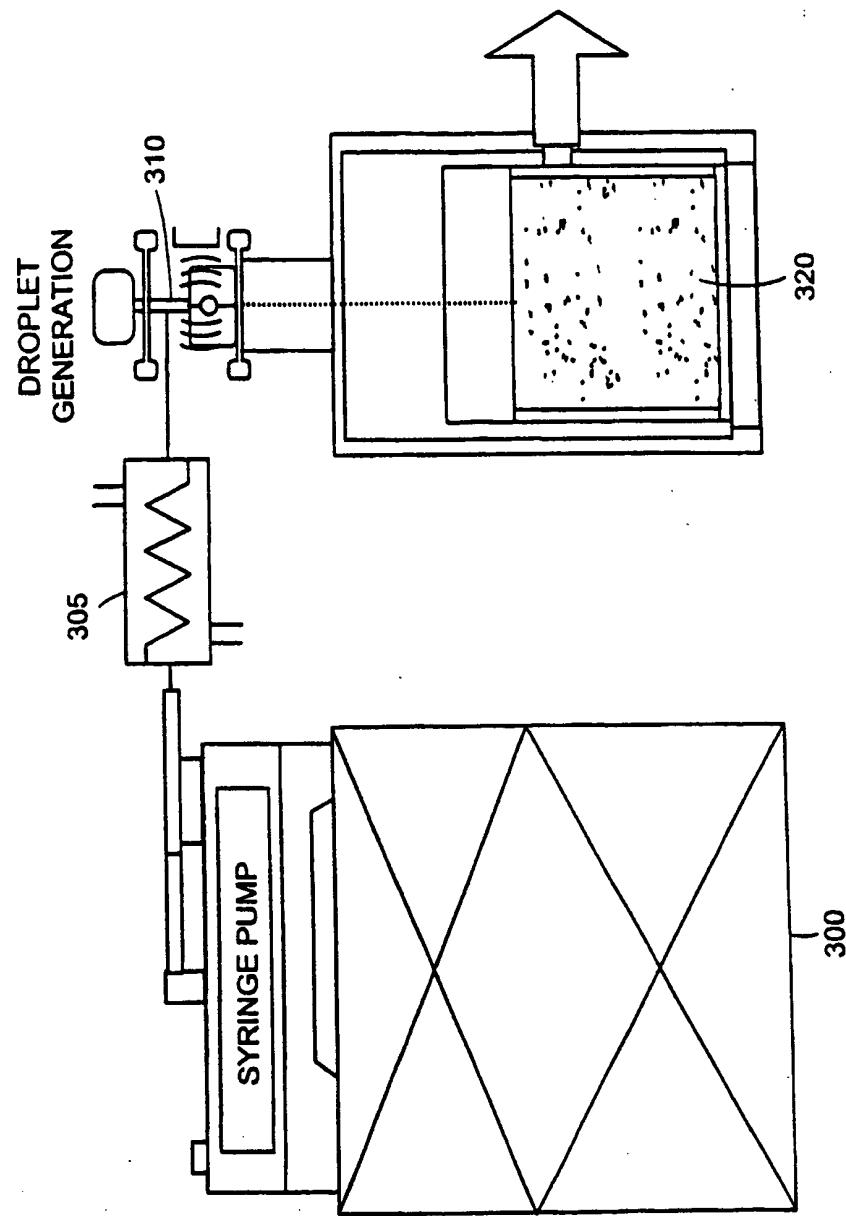


FIG. 4B

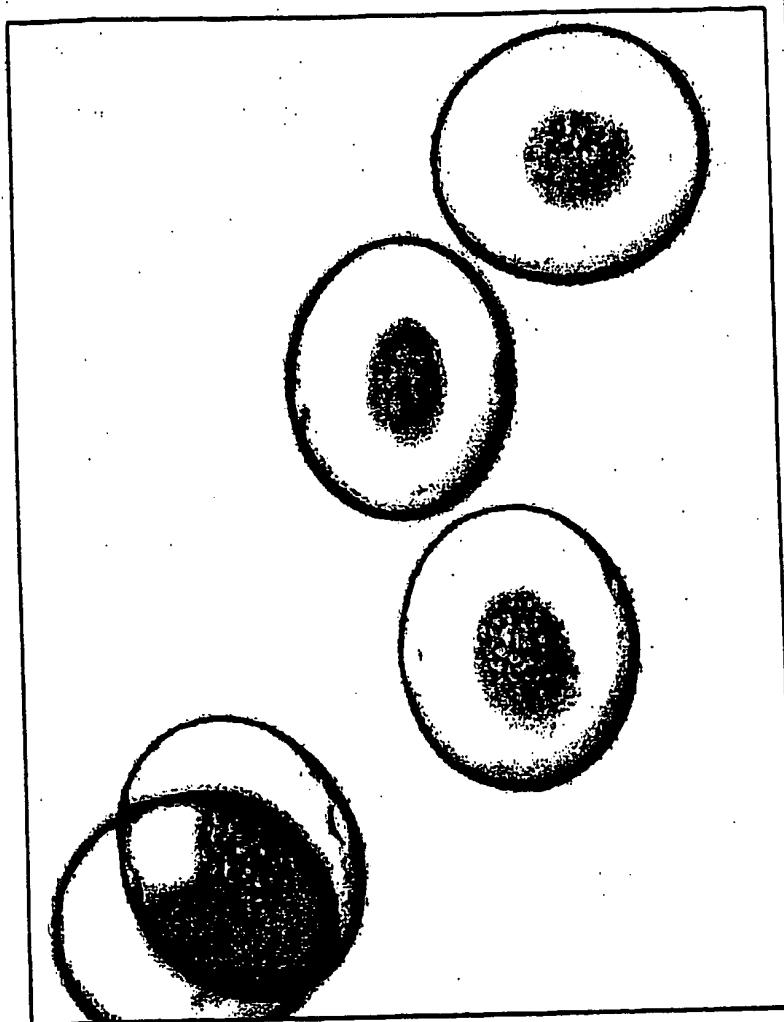


FIG. 5

ECA DIAMETER DIFFERENTIAL VOLUME
600.0 - 1400.0 MICRONS

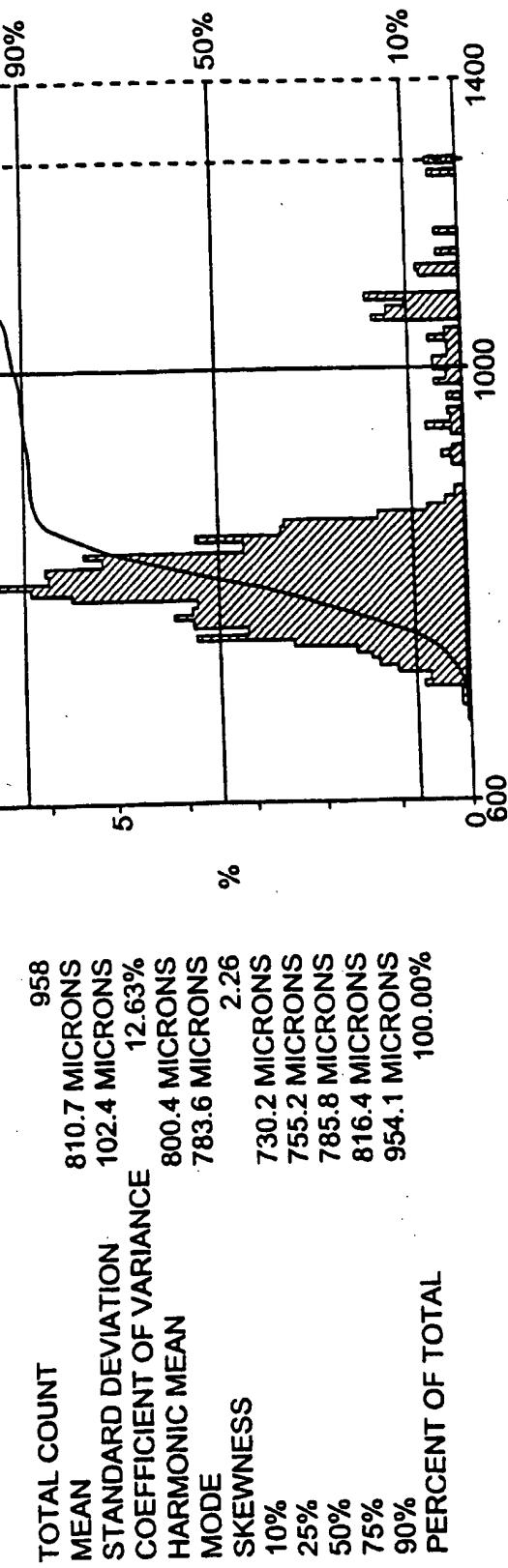


FIG. 6

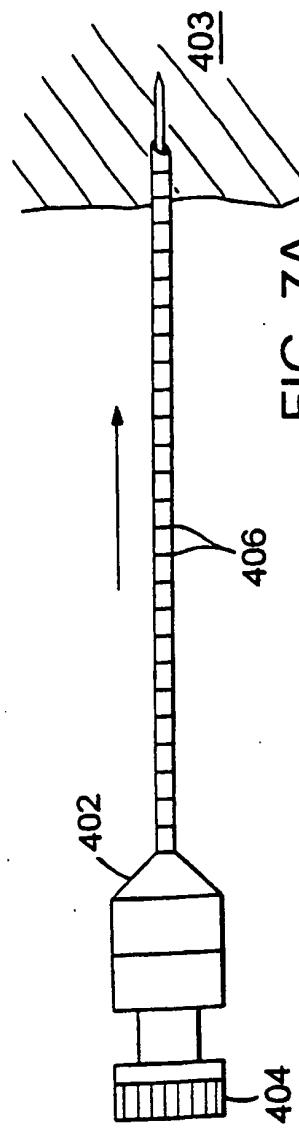


FIG. 7A

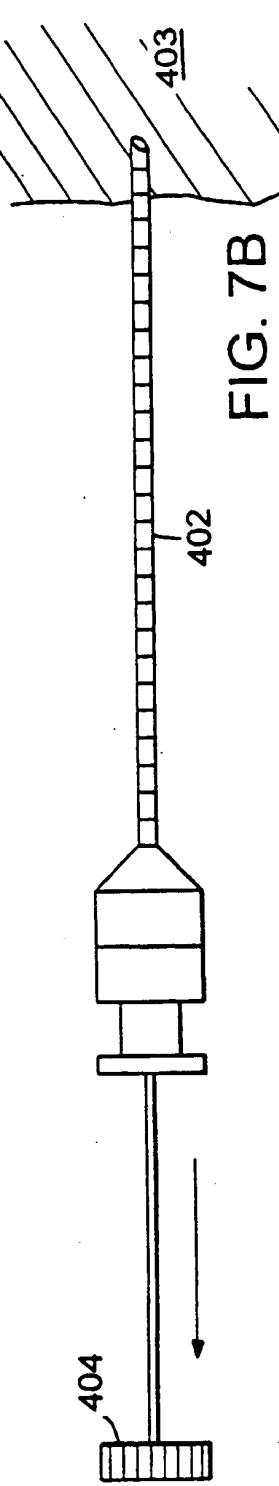


FIG. 7B

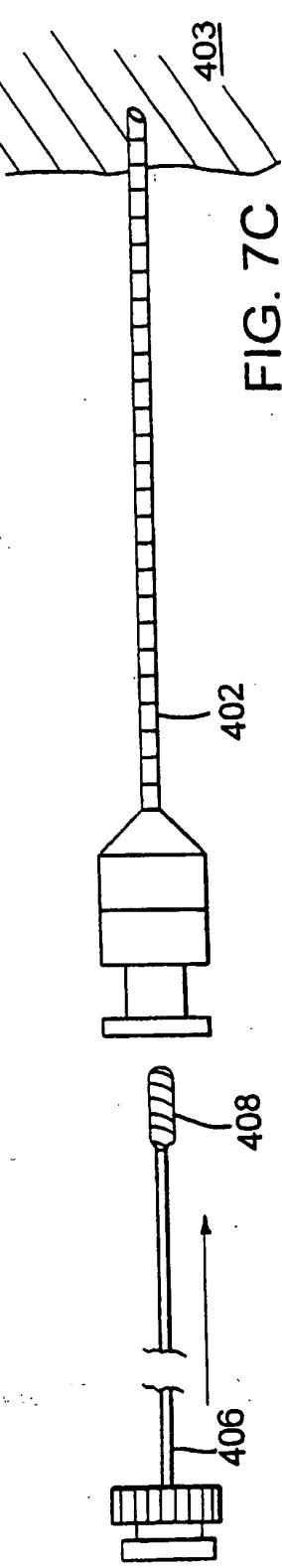


FIG. 7C

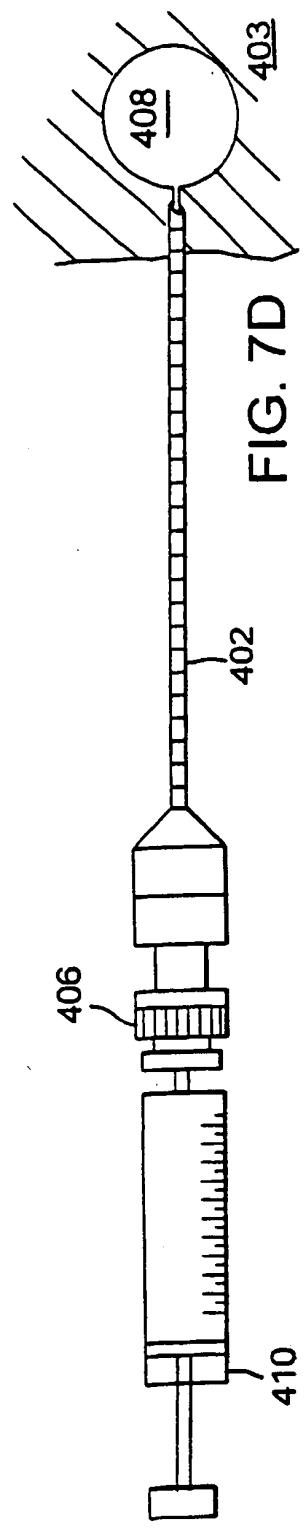


FIG. 7D

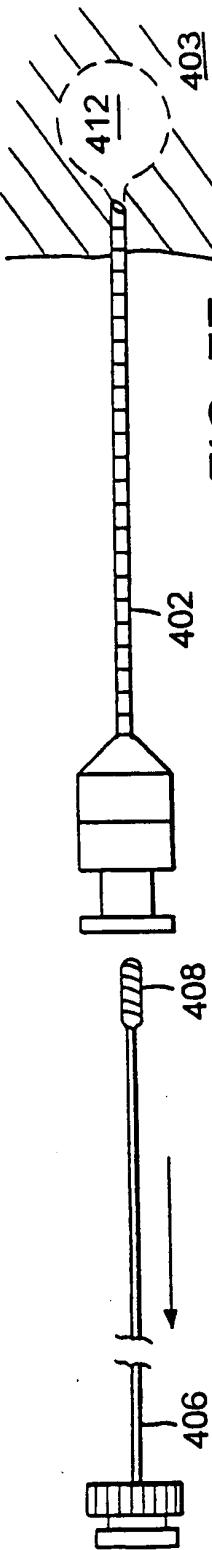


FIG. 7E

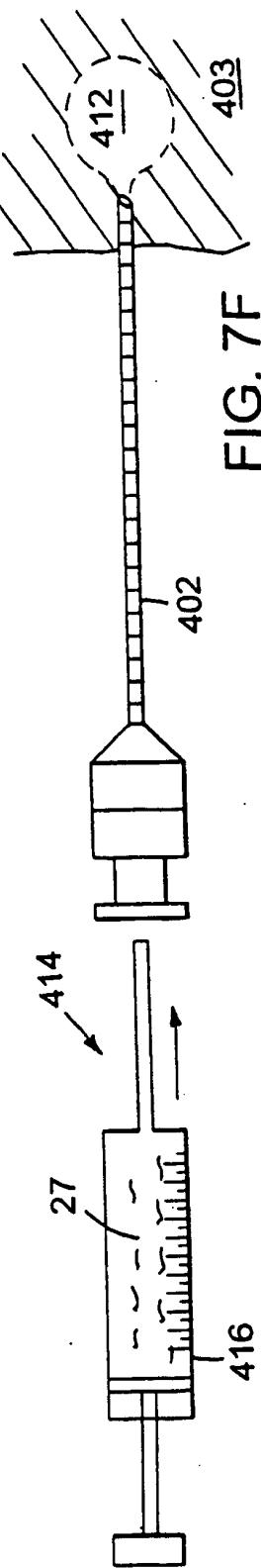


FIG. 7F

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/09467

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61L24/04 A61L24/00 A61L27/50 A61L27/16 A61L31/04
 A61L31/14 A61F2/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61L A61F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EMBASE, EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | US 2001/051670 A1 (ASFAW BRUKTAWIT T ET AL) 13 December 2001 (2001-12-13) page 8; claims --- | 1-25 |
| X | YUSI G M ET AL: "Submucosal injection of polyvinyl alcohol in artificially created vesico-ureteral reflux: A preliminary report" ASIAN JOURNAL OF SURGERY 1995 HONG KONG, vol. 18, no. 2, 1995, pages 122-127, XP008020559 ISSN: 1015-9584 abstract --- | 1-10, 14, 15 |
| X | US 6 315 709 B1 (GARIBALDI JEFF ET AL) 13 November 2001 (2001-11-13) claims --- | 1-10 -/- |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

7 August 2003

Date of mailing of the international search report

22/08/2003

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/09467

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| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/09467

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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